ON THE AFFECTIONS CLINICALLY SIMULATING TYPHOID FEVER, WITH ESPECIAL REFERENCE TO AND REPORTS OF CASES OF BRILL'S DISEASE

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ATTESTING to the evolution in clinical observation which our present knowledge of the differentiation of the exanthemata represents are the historical facts[1] that from Sydenham's time up to the beginning of the eighteenth century the term scarlet fever was applied to no less than four distinct diseases and that only about seventy-five years ago was the distinction recognized between typhus and typhoid fever. Owing largely to important bacteriological investigations in which Gärtner[2] in 1888 was the pioneer, the terminology of the older writers as to exceptional cases of typhoid fever began to undergo changes. Thus the appellation "abortive typhoid" was often replaced by "food poisoning" and some of the outbreaks previously regarded as "mild typhoid" were differentiated as epidemics of "paratyphoid fever." Based on interpretations of distinctive clinical and negative bacteriological evidences a further advance is the relegation into a separate though unclassifiable group of a fairly common condition which has previously been regarded as atypical typhoid fever.

Some of the acute infectious diseases which oc-

casionally assume a temporary clinical picture of typhoid fever are miliary tuberculosis, septic endocarditis, malaria, influenza and the meningitides. Let us disregard this casual simulation in a *tentative classification* of the conditions which frequently bear more or less clinical resemblance to typhoid fever: (1) Intestinal Sapremia. (2) Coli Infections. (3) Meat Poisoning. (4) Paratyphoid Fever. (5) Brill's Disease.

1. *Intestinal Sapremia.*—In conditions of marked constipation, headache, apathy, a dry furred tongue, anorexia, prostration, abdominal pain, sustained temperature elevation, palpable spleen and an eruption may all be present to suggest the possible existence of typhoid fever. The eruption is, however, profuse and blotchy, macular and erythematous, and is not likely to be mistaken for a roseola nor for the eruption peculiar to Brill's disease (*vide infra*). Moreover, the administration of a brisk saline purge causes prompt defervescence and rapid disappearance of the rash. If, however, the duration of symptoms is not definitely ascertainable, or if they have been of longer duration than usual, the suspicion of typhoid fever may make active catharsis inadvisable. Such circumstances have been known by the writer to prolong for a week or more the ultimate exclusion of typhoid fever by means of the clinial course and the diagnostic aids of the laboratory.

2. *Coli Infections.*—Cases of aggravated constipation exhibiting typhoidal symptoms are occasionally met with in which isolation from the urine and blood of the *Bacillus coli communis* or positive and exclusive agglutination of the patient's serum against most strains of this organism prove these exceptional cases to be a general coli infection

rather than an intestinal sapremia.[3] An epidemic of this nature has been reported in Bavaria.[4]

Sanarelli has shown that the bacillus coli in the intestine increases in number and virulence in typhoid fever.[5] Moreover, the serum of typhoid patients frequently gives an agglutinative reaction with races of *Bacillus coli;* and a bacteriuria in typhoid fever shows the presence of this organism in the urine.[1] The clarification of the exact relationship of the *Bacillus coli* to typhoid fever is a problem for future solution.

3. *Meat Poisoning.*—In the outbreaks of meat poisoning which occur from time to time the clinical course of the disease varies considerably. In many of the cases the symptoms suggest a simple gastroenteritis; some of the severer cases resemble cholera nostras; while still other cases bear clinical as well as pathological resemblances to typhoid fever.[6] In the last type differentiation from typhoid fever has been made practicable by the discovery of the efficient cause, which is either Gärtner's enteritidis bacillus, or the *Bacillus paratyphosus B.* Both of these organisms can be distinguished biologically from the colon bacillus and the *Bacillus typhosus;* and recent studies have conclusively shown that the serum of patients ill with meat poisoning regularly agglutinates known cultures of the causative organism.[7]

Poisoning caused by the proteus or colon bacillus in decayed meat and certain other forms of bacterial food poisoning have not been touched upon for the reason that the symptoms produced are not likely to be mistaken for those of typhoid fever.

4. *Paratyphoid Fever.*—That there exists at least one infectious disease not caused by the Eberth bacillus though materially componental of the pre-

viously so-called typhoid fever was firmly established nearly a decade ago by the studies of Achard and Bensuade, Widal, Gwyn, Durham, Cushing, Schottmüller, Coleman and Buxton, Meltzer, and others.[8] An important and more recent contribution to the literature of this subject is that of Herbert Fox.[9]

Indistinguishable clinically from typhoid fever, and occurring both sporadically and in epidemics, paratyphoid fever can be diagnosed only with the aid of the bacteriologist, who must isolate from the blood, urine or feces the paratyphoid bacillus, or else obtain properly controlled positive agglutination reactions against this organism either (preferably) with the serum of a highly immunized animal or with the patient's serum. In bacteriological investigations of epidemics abroad the *Bacillus paratyphosus B.,* is recovered much more frequently than the *Bacillus paratyphosus A.,* while in America the reverse seems to hold true.[9] Thus Proescher and Roddy have reported forty-eight cases of type A paratyphoid occurring in Allegheny.[10] Recently, however, in an epidemic in Virginia, agglutination tests were positive exclusively against the *Bacillus paratyphosus B.*[11] In another recent epidemic in a barracks in France similar results were obtained after the *Bacillus paratyphosus B.* had been isolated from the blood in seven of the eight cases in which cultures were made.[12] There is still some uncertainty, however, as to the diagnotic accuracy of such serum reactions without other definite bacteriological proof as to etiology. Occasionally, as in Libman's celebrated case,[13] the serum of a patient from whose blood a paratyphoid bacillus has been isolated will agglutinate, not only this organism, but also the

Bacillus typhosus in low dilutions. Interesting are the facts that immunity from paratyphoid is not conferred by a previous attack of typhoid and that there is a paratyphoid cholecystitis similar to that complicating typhoid fever.[14]

Because of the etiological relationship of the *Bacillus paratyphosus B.* to certain forms of bacterial food poisoning, the question arises whether there is a common infectious disease assuming an acute form as meat poisoning and a subacute form as paratyphoid fever. Some of these problems will probably be solved by the continued studies of competent bacteriologists such as the recent painstaking investigations of Proescher and Roddy.[7]

5. *Brill's Disease.*—Because of the complex symtomatology and protean typology of typhoid fever caution should be exercised before stating that an affection bearing clinical resemblance to atypical typhoid fever is not the same disease, especially if the condition has hitherto remained unrecognized by all internists except N. E. Brill and by all pathologists except E. Libman. In no spirit of disapprobation be it said that both of these observers have taken advantage of and have been able to evolve a new disease from the criteria born of scientific exactness and bacteriological scrutiny which now limit the scope of the term typhoid fever. Fortunately all authorities are now agreed as to certain criteria based upon the following facts: (*a*) the Widal reaction is present in about 95 per cent of all cases; (*b*) the Eberth bacillus can be isolated from the blood in over 90 per cent of all cases; and (*c*) the roseola is an almost constant sign. If, therefore, in a large number of cases the true roseolar eruption is regularly absent and the blood culture and Widal are regularly negative, we are justified in conclud-

ing that the great majority of these cases, to say the least, are not typhoid fever. Similar negative evidence with reference to the paratyphoid roseola and the paratyphoid organisms and agglutination reaction also establishes the exclusion of paratyphoid fever. Furthermore, if there are definite and constant clinical characteristics in the cases referred to distinguishing them from typhoid and paratyphoid fever, such a deduction is indisputably warrantable.

Every practical clinician of to-day, provided that he has fair training, experience and acumen, must recollect having at one time or another treated what passed for atypical typhoid fever—not, however, without the conviction that he was not actually dealing with typhoid. That this is true is shown by the following incident. The house physician at Beth Israel Hospital had suggested influenza as a discharge diagnosis, and on being questioned as to the propriety of this designation, Dr. S. Horwitt replied that he knew the case was not really influenza, but that the system of nomenclature in vogue at this hospital (the Bellevue system) excluded vague terms like autointoxication; and furthermore that though the condition resembled typhoid or paratyphoid somewhat, neither of these appellations would be justifiable. The interne's response demonstrated his recognition of an unclassifiable condition, which in fact was a typical case of the disease which we have called Brill's disease in spite of the undesirability of eponymic nomenclature.

For a detailed description of this affection the reader is referred to Brill's convincing and comprehensive presentation of the subject in the *American Journal of the Medical Sciences* for April, 1910,[15] and for a critical survey to an editorial in

the MEDICAL RECORD for April 30, 1910.[16] In this communication we shall limit ourselves to: (*a*) a justification of the proposed admittance into medical nosography of this affection; (*b*) remarks on the facility and practical importance of differentiating it from typhoid fever; and (*c*) reports of three cases.

As early as 1896 Brill had "noticed a type of disease somewhat similar, but characteristized by many features irreconcilable to the picture of typhoid fever;"[15] and two years later Brill published "A Study of Seventeen Cases of a Disease Clinically Resembling Typhoid Fever, but Without the Widal Reaction."[17] These studies have been continued ever since with the best obtainable laboratory facilities for agglutination tests and blood, stool and urine cultures, all of which were most systematically carried out with the last fifty cases of Brill's series, and have proven that "the affection has nothing in common with typhoid, paratyphoid and typhoid-colon or intermediate group infections."[15] In 1906, speaking before the Johns Hopkins Hospital Medical Society, E. Libman stated that "in the group of cases described by Dr. Brill, which resemble typhoid fever somewhat, and which have been considered to have been possibly cases of paratyphoid fever, we could not succeed in isolating any organisms from the blood. There is no proof as yet that they are cases of paratyphoid, and should, therefore, be classed for the present as a *separate group*."[18]

The discussion following Dr. Brill's original presentation of this subject before the Section on Medicine of the New York Academy of Medicine evinced a hesitancy to accept as a newly discovered disease a condition for which there existed only

negative bacteriological and pathological evidence. Some of the participants in this criticism seemed to be oblivious of the fact that medical nosology was well established before the advent of the bacteriologist. Were his services required to distinguish measles from scarlet fever, typhoid fever from typhus, and infantile scurvy from rheumatism?

It is no exaggeration to state that the clinical differences between Brill's disease and typhoid fever are so pronounced and easy of recognition that the practical differentiation is less difficult than that between German measles and measles or that between German measles and scarlet fever. Let us now consider these differences seriatim.

The most striking mark of differentiation is the *eruption,* which appears as a single crop usually before the seventh day of the disease. There are no new crops. Appearing first on the abdomen and back, the rash spreads rapidly to the chest wall and extremities, is sometimes seen on the neck, palms and soles, and is often more profuse on the upper extremities than on the trunk. The rash is a profuse one and sometimes a number of the lesions run together to form small patches. The spots are maculopapular in character and usually have an oval, indistinct outline. On stretching the skin or making pressure over the spots, the latter fade somewhat but do not disappear entirely. Sometimes hemorrhagic spots are seen interspersed with the other lesions and frequently there are present in addition suspicious but not typical roseolæ. The eruption fades rapidly at the time of defervescence, but its remains are seen for some days in the form of brownish stains.

The febrile invasion is usually abrupt and is ushered in with a chill or chilly sensations followed

by very severe headache and high fever. For a variable period previous to the invasion there is general malaise. The temperature curve reaches its acme in about three days and then remains sustained till the time of crisis or rapid lysis (see temperature charts of illustrative cases). While the fever lasts the headache persists severe and in a small proportion of cases there is also meningismus. Apathy and prostration develop very early, and the patient ill with Brill's disease looks as poisoned and as sick in the first week as does the typhoid patient in the second or third week.

Just as distinctive as the eruption is the *prompt recovery of the patient at the time of defervescence.* After the temperature has remained continuously high for a period varying from one to two weeks, there is a fall to normal in from ten to sixty hours; thereafter, in the great majority of cases, the temperature never again rises above normal. No case has been observed with a relapse or with serious sequelæ, and the mortality is nil. At the time of crisis or rapid lysis, the mental condition becomes bright, the headache disappears and the patient says that he is entirely well. It is usually difficult and apparently unnecessary to keep the patient in bed for as long as a week after the temperature has fallen. Characteristic is this rapid convalescence to complete recovery.

A leucopenia in this disease is exceptional. Usually the absolute and differential leucocyte count is normal.

The negative agglutination reactions and negative blood, stool, and urine cultures have already been dwelt upon.

The uniformity of the symptoms, the distinctive features mentioned above and their unlikeness to

comparable manifestations in typhoid and paratyphoid fever make the diagnosis comparatively easy. Moreover, with the help of the characteristic eruption the diagnosis can be made early in the course of the disease, a fact which from a prognostic standpoint is of great practical significance to the practitioner. Is it not a boon when a patient is apparently seriously ill with a febrile disease to be able to predict with a fair measure of certainty that the patient will be up and about in between two and three weeks and that recovery will be complete?

Speculations will not be indulged in as to the pathogenesis, about which practically nothing is known. Clinically the disease bears more resemblance to mild typhus fever than it does to typhoid. Brill states that during an epidemic of typhus differentiation from mild cases would probably be impossible. Yet Brill is firmly of the opinion that the disease is *not* typhus. Against the view that Brill's disease is typhus modified and attenuated by importation, new environment or other changed conditions are its nonepidemic occurrence, its usual noncommunicability, its uniform clinical picture, and the absence of grave and fatal cases. Immunity from Brill's disease is not conferred by a previous attack of typhoid fever. Since there are apparently periods of incubation, invasion, continued fever, and decline, by analogy the designation "infectious" is justifiable. There is little evidence to indicate that the disease is communicable. In Brill's 221 cases members of the same family or occupants of the same house were never attacked. Warren Coleman has, however, observed four cases from the same family and same household—cases in which Dr. Brill concurred in the diagnosis.

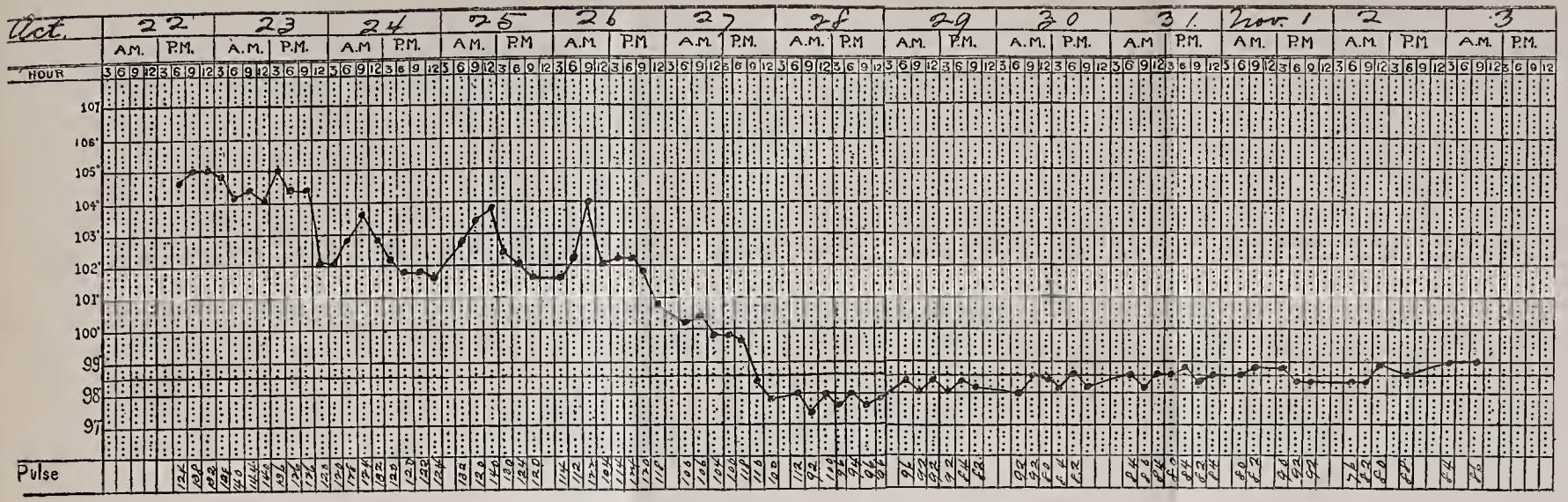

CHART I.—Temperature curve in Brill's disease. (See Case I.)

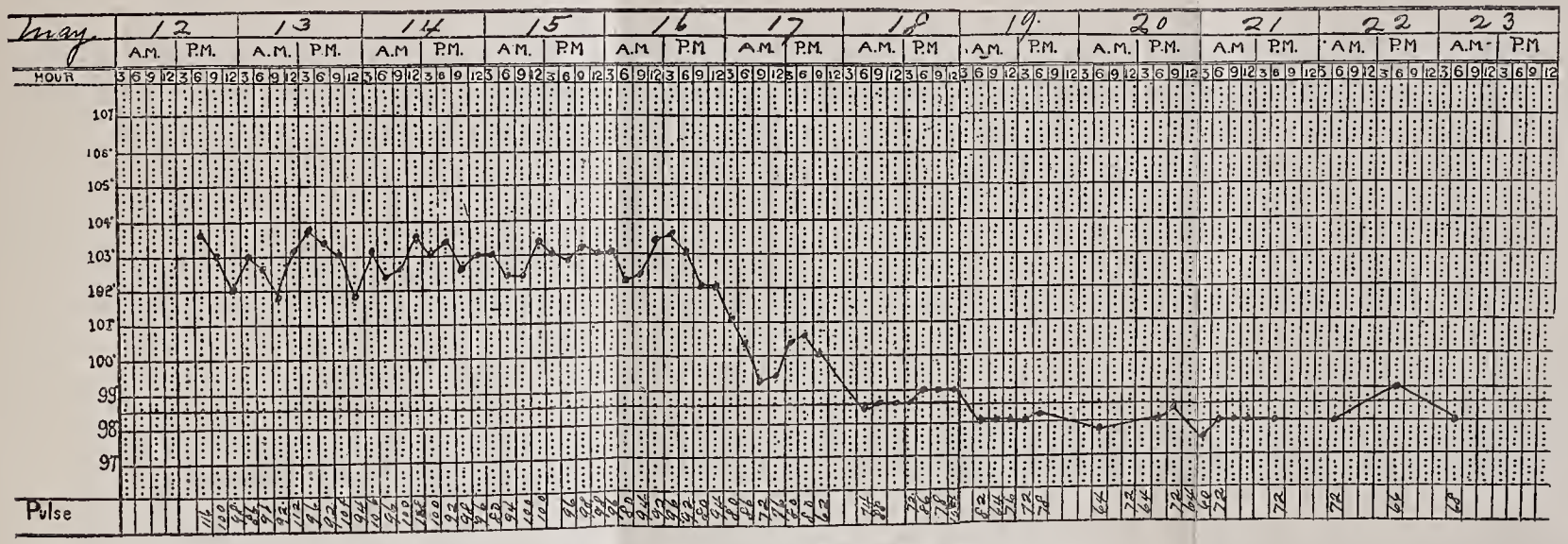

CHART II.—Temperature curve in Brill's disease (See Case II.).

The following case reports are submitted with the hope of aiding in the general recognition of this interesting affection, for which we know no better name than Brill's disease:

Case I.—A woman 29 years of age, born in Russia, was admitted on October 22, 1909, to the service of Dr. J. E. Reinthaler at Beth Israel Hospital. Married when 16 years old, she had had five children who were alive and well. The present illness began suddenly five days before admission with a chill followed by high fever. Since the onset there were severe headache, anorexia, prostration, fever and diarrhea (about six bowel movements a day). On admission the temperature was 104.6°. There was a profuse maculopapular eruption spread over the trunk and extremities with suspicious roseolæ interspersed amongst the other lesions. The patient was well nourished and well developed but greatly prostrated. The skin was hot and dry. The pharynx was congested. The pulse was not dicrotic. The spleen was not palpable. The course of the temperature curve is shown in Chart I. Five leucocyte counts averaged 10,200 with an average polymorphonuclear count of 70 per cent. The diazo reaction was positive; otherwise the urine was negative. On the 10th and 11th days of the illness the temperature dropped within 30 hours to subnormal, was subnormal for 24 hours, and then remained normal. Repeated Widal reactions were negative and a blood culture performed on the ninth day of the disease by Dr. J. J. Hertz was negative. Recovery was rapid and the patient was out of bed one week after defervescence.

Case II.—A man 25 years of age, unmarried, a native of Russia, was admitted on May 12, 1910, to the service of Dr. A. H. Friedenberg at Beth

Israel Hospital. Twelve days before admission there developed general malaise, anorexia, and constipation; these symptoms continued for nine days and then the patient took to his bed because of the development of chilliness, fever, headache, and prostration. The temperature on admission was 103.6°. The pulse was dicrotic. Though well nourished and robust, the patient was markedly apathetic and prostrated. The tongue was moist and uniformly coated. The skin was hot and dry. A profuse maculopapular eruption, hemorrhagic in areas, was scattered over the abdomen, back, chest wall and extremities. The spots were of a dull red color and not completely effaced on stretching or making pressure over the skin. In certain areas a number of spots ran together to form small patches. There were numerous lesions on the forearms and a small number on both soles. Otherwise physical examination was negative. The spleen was not palpable. The temperature remained sustained (see Chart II), never more than one degree above or below 103, until the ninth day, when it fell to normal within 36 hours and remained so. The symptoms during the febrile period were severe headache, apathy, prostration, anorexia and constipation. No new lesions appeared on the skin during the time of observation and the original crops faded rapidly at the time of defervescence. On the seventh and eighth days of the disease the headache was extreme, and there developed moderate rigidity of the neck and slight Kernig's sign. The meningismus disappeared at the time of crisis. The absolute and differential leucocyte counts were normal. The urine was negative. Repeated Widals during and after the febrile course were negative. A blood culture performed on May 16th, by Dr. J. J. Hertz,

was negative. Recovery was rapid and uninterrupted.

Case III.—A married Russian woman 41 years of age, with six living children, was admitted on March 29, 1909, to the service of Dr. A. H. Friedenberg at Beth Israel Hospital. Having had no serious illness previously, the present one began ten days before admission with chilliness, fever, severe headache, general pains and prostration. There had been general malaise for some days previous to this onset. On admission the temperature was 105°, the pulse 110. The tongue was dry and red, the throat was congested. There was slight rigidity of the neck, no Kernig's sign. A profuse maculopapular eruption was scattered over the trunk, neck and extremities. The spleen was palpably enlarged. The patient was somnolent, markedly prostrated and complained of severe headache. Otherwise physical examination was negative. The temperature remained elevated above 102° till the thirteenth day of the illness, when it dropped to normal within 60 hours and thereafter remained normal. A blood culture performed on the thirteenth day of the disease was negative. Frequently repeated Widals continued after defervescence were negative. As the temperature dropped the headache disappeared, the mental condition became brighter, the appetite returned and the patient was up and about six days after defervescence.

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